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REVIEW

The history of 0.9% saline

Sherif Awad, Simon P. Allison, Dileep N. Lobo*

Division of Gastrointestinal Surgery, Wolfson Digestive Diseases Centre, Nottingham University Hospitals, Queen's Medical Centre, Nottingham NG7 2UH, UK

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Summary
Background & aims: We aimed to trace the historical origins of 0.9% saline, how it came to be used so commonly today, and to consider whether its continued use can be justified.
Methods: We searched the Medline, Science Citation Index, ScienceDirect and Google™ databases using the key words saline, physiological, salt solution, sodium chloride, 0.9%, intravenous, injection, fluid, cholera, resuscitation, parenteral, history, historical and origins.
Results: The use of 0.9% saline is believed to have originated during the cholera pandemic that swept across Europe in 1831. However, an examination of the composition of the fluids used by the pioneering physicians of that era reveals solutions that bear no resemblance to 0.9% or so-called 'normal' saline which appears to have very little scientific or historical basis for its routine use, except for Hamburger's *in vitro* studies of red cell lysis.
Conclusions: The currently used 0.9% saline solution is without convincing historical basis. Given that the composition of 0.9% sodium chloride is dissimilar to most solutions used in the past, and is in no way 'normal' or 'physiological', our current practice may be based on historical fallacy and misconception.

Introduction

Each year nearly 10 million litres of 0.9% sodium chloride (saline) are infused intravenously in the UK (data from Baxter Healthcare, UK). Despite being one of the most frequently used crystalloids for resuscitation, replacement and maintenance, the origins of 0.9% saline remain obscure.

The use of saline is believed to have originated during the cholera pandemic that swept across Europe and reached England in 1831.[1–9] However, the solutions used by Latta,[10] Jennings[11] and other pioneers of that era show little similarity to 0.9% saline. How, therefore, did 0.9% saline come into use and when did it become accepted as 'normal' or 'physiological'? The aims of this review are to

* Corresponding author. Division of Gastrointestinal Surgery, E Floor, West Block, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, NG7 2UH, UK. Tel.: +44 115 8231149; fax: +44 115 8231160.
E-mail address: dileep.lobo@nottingham.ac.uk (D.N. Lobo).

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trace the historical origins of 0.9% saline, how it came to be used so commonly today, and to consider the justification for its continued use.

Search strategy

We performed internet-based searches of the Medline (Ovid, PubMed, Embase) and Science Citation Index databases, historical journals on ScienceDirect and the Google™ search engine using the key words saline, physiological, salt solution, sodium chloride, 0.9%, intravenous, injection, fluid, cholera, resuscitation, parenteral, history, historical and origins in various combinations with the Boolean operators AND, OR and NOT. We also hand searched key journals, medical history textbooks and the reference lists of key articles.

Early history: the arrival of cholera

The Indian Blue Cholera pandemic reached Sunderland in northeast England in October 1831 and stimulated the first developments in intravenous fluid therapy. Owing to the limited knowledge base at the time, 76 different and ineffective or damaging treatments were advocated for cholera,[12] including bloodletting as a means of ''diminishing the venous congestion'', emesis to rid the body of ''poisons'' and the inhalation of the protoxide of azote (laughing gas, nitrous oxide) to ''remedy the absence of arterialisation''.[13]

A year earlier in Moscow, Hermann, a chemist at the Institute of Artificial Mineral Waters, analysing the blood of cholera patients found it to have lost as much as 28% of its fluidity. He concluded that ''the liquids evacuated in cholera ... form constituent parts of the blood, which is deconstituted by their disappearance ... consequently the thickening of the blood ... prevents its circulation''. He, therefore, argued for treatment to reduce the evacuations responsible for the loss of fluid.[3] Hermann's colleague, Jachnichen injected 6 oz of water intravenously into a cholera patient, whose pulse returned for a quarter of an hour, although he died two hours later.[3,14,15]

In 1832 William Stevens observed that the blood of patients with yellow fever was darker than normal and could be restored to its red colour by administering oral solutions of ''non-purgative neutral salts''.[16] Although reported to have treated cholera patients with his 'saline plan' Stevens' aim was not rehydration, but restoration of the blood to its red colour.

In his seminal paper published in the Lancet on 10th December 1831, William Brooke O'Shaughnessy, at the age of 22, having just graduated from Edinburgh Medical School, proposed a new method of treating cholera ''by the injection of highly-oxygenated salts into the venous system''.[13] O'Shaughnessy noted the effects of cholera were the ''universal stagnation of the venous system, and rapid cessation of the arterialisation of the blood''. He hypothesised that ''if we could bring certain salts of highly oxygenated constitution fairly into contact with the black blood of cholera, we could certainly restore its arterial properties ... I therefore conceived the idea of injecting into the veins such substances ... most capable of restoring it to the arterial qualities''. He recommended injection into the veins ''of the salts which contain the greatest quantity of oxygen, and possess most powerfully the action of oxidising venous blood ... the nitrate or chlorate of potash''. Having trialled his proposal on a dog, with no ill effects, he recommended his method be used ''in the fearful cases in which venesection is found impossible''.

O'Shaughnessy then travelled to Sunderland to study the disease[17] and submitted a preliminary report to the Lancet detailing his experiments on the blood in cholera.[18] His report to the Central Board of Health of London was also later reviewed by the Lancet.[19] Having presented a critical examination of the work of Hermann and Stevens, he reached the following conclusions concerning the aim of treatment: ''1st, to restore the blood to its natural specific gravity; 2nd, to restore its deficient saline matters. The first of these can only be effected by absorption, by imbibition, or by the injection of aqueous fluid into the veins. The same remarks, with sufficiently obvious modifications, apply to the second.'' He recommended injection into the veins of tepid water holding a solution of the normal salts of the blood. The reviewer[19] went on to say of O'Shaughnessy ''his experiments having, we presume, led him to abandon his former ideas respecting the superior efficacy of highly oxygenated salts''. It was clear, therefore, that by this time O'Shaughnessy had made the intellectual leap from his oxygenation theory to realising the primacy of salt and water replacement.

The evolution of saline solutions

Less than 7 weeks following O'Shaughnessy's recommendations[19] the first cases of cholera were treated with intravenous saline solutions. Robert Lewins, a physician in Leith, Edinburgh, reported the results of this new treatment to the Central Board of Health in London and published them in the Lancet of 26th May 1832.[20] He describes witnessing this treatment in three of six patients treated by Thomas Latta to whom he ascribes the ''merit of first having recourse to this practice''. Lewins described the immediate effects of injection as ''restoring the natural current in the veins and arteries, of improving the colour of the blood, and recovering the functions of the lungs'' as ''the most wonderful and satisfactory effect'' and recommended repeated injections of large quantities of solution guided by the patient's pulse and symptoms, thereby showing a remarkably modern understanding of the need for continuous treatment guided by physiological monitoring.

The solution used by Latta, according to Lewins,[20] consisted of ''two drachms of muriate, and two scruples of carbonate, of soda, to sixty ounces of water'', a different composition to that reported by Latta in his detailed letter to the Central Board of Health a week later, in which he outlined his rationale for using salt solutions and the results of treatment.[10] Latta, having read O'Shaughnessy's analyses, attempted to ''restore the blood to its natural state'' by administration of oral saline solutions only to find that this aggravated the symptoms of vomiting and purging.

He, therefore, ''proceeded to throw the fluid immediately into the circulation'' and, with ''no precedent to direct'' him, used ''two to three drachms of muriate of soda and two scruples of the subcarbonate of soda in six pints of water''.[10] He followed this with a description of the initial four cases treated: an aged female who had ''reached the last moments of her earthly existence'', a female of 50 and ''very destitute'' and a ''delicate young female, of strumous habit''. Three of the four patients died and Latta attributed the deaths to ''deficiency in quantity'' of saline injected, the presence of organic disease and the ''late application of the remedy''.

Further reports from Lewins[21] and Craigie[22] detailed the treatment of more cholera patients at the Drummond Street Hospital in Edinburgh. In the former, three of six patients survived, and in the latter one of two survived. Craigie's solution[22] consisted of one drachm muriate of soda, ten grains carbonate of soda in two pounds *aqua calid* and was again different from those described previously.

Murphy,[23] Macintosh[24] and Anderson[25] also reported trials of intravenous salt solutions, but without describing their composition. Controversially, Murphy claimed that the idea of making ''an artificial serum ... to throw ... in by the veins'' had occurred to him three weeks prior to Latta's seminal publication in the Lancet of 2nd June 1832[10] and cited two witnesses in testimony.

Although the declared aim was to replace the fluid losses of cholera with solutions as close in composition as possible to that of serum,[20] all the early solutions used were hypotonic. However, given that medical chemistry was in its infancy at that time, it is remarkable that these physicians showed such insight into the treatment of this invariably fatal illness.

Composition of salt solutions

To understand how a concentration of 0.9% saline came into general use, a hand-search was undertaken of the literature from the 19th and early 20th centuries. The constituents of the solutions were described in traditional chemical terms (Table 1) and apothecary's measures (Table 2). We have recalculated the composition of the various solutions[3,6,10,20,22,26–41] and have expressed the ionic composition in mmol/l (Table 3).

It was Latta in 1832 who, having modified his original solutions, devised one most closely resembling the concentration of electrolytes seen in blood.[31] This solution containing sodium 134 mmol/l Na^+, 118 mmol/l Cl^- and 16 mmol/l HCO_3^- was closer to the composition of plasma and, therefore, more 'physiological' than 0.9% saline. Despite this, Latta's solution was not adopted by his contemporaries who made no further reference to it. Indeed, no solution of similarly physiological composition was described until that of Sydney Ringer 50 years later[37,42] (Table 3). A possible explanation for this may be Latta's death from pulmonary tuberculosis in 1833.[1]

Table 1 Modern equivalents of traditionally used terms

Traditional name	Modern equivalent
Muriate of soda, common salt	Sodium chloride
Carbonate of soda	Sodium carbonate
Subcarbonate of soda	Sodium bicarbonate
Aqua calid	Hot water
Sulphate of potash	Potassium sulphate
Phosphate of soda	Sodium phosphate
Protoxide of azote	Nitrous oxide

Table 2 Conversion of apothecary's measures to metric equivalents

Traditional unit	Metric equivalent
Weight	
Grain	0.065 g
Scruple (20 grains)	1.295 g
Drachm/dram (3 scruples)	3.887 g
Ounce (8 drachms)	31.104 g
Pound (12 ounces)	373.241 g
Volume	
Drachm/dram	3.552 ml
Ounce (8 drachms)	28.413 ml
Pint (20 ounces)	568.261 ml
Quart (2 pints)	1136.522 ml

Dissent in the medical profession: saline treatment does not prosper

Having heard of the use of intravenous saline injections by Latta and Lewins, O'Shaughnessy thought the results exceeded his ''most sanguine expectations''.[43] Supporters of this new treatment, however, were few and articles describing the failure of saline injections appeared.[44–46] Latta felt the need to defend his practice against ''members in the profession guilty of scribbling on medical subjects in the newspapers of the day'' and felt ''this was a crime for which they have no excuse''.[47] Latta referred to Craigie who had written to a newspaper claiming credit for discovering the new treatment and went on to cite the main reason for any failures of his treatment as the delay in its use until the disease was too far advanced and all other treatments had failed. Even some of his survivors were initially moribund with ''the pulse gone, even in the axilla''.

Although Latta understood the need for repeated injections guided by the response to treatment,[10] many of his contemporaries did not and therefore under-treated their patients. Other reasons for the failure of saline treatment include the use of hypotonic fluids causing haemolysis, infection due to the lack of sterility of the fluids and equipment then in use, and inadvertent air embolism.[48]

With the loss of saline's two main proponents through the death of Latta and O'Shaughnessy's departure to India in 1833, and with the end of the cholera epidemic in England, there was a danger that saline would be confined to the history books. Fortunately, advances in circulatory physiology in the mid-19th century,[6] and the discovery of the resuscitative effects of saline solutions in haemorrhage[11,40,41] and trauma[26] led to a resurgence of interest.

Table 3 Composition of early saline solutions

Name of solution	Constituents	Modern equivalents	Modern equivalents, mmol/ l of solution
1832: Latta's solution 1[20]	2 drachms muriate of soda, 2 scruples carbonate of soda, 60 ounces of water	Na^+ 180 mmol, Cl^- 133 mmol, CO_3^{2-} 24 mmol, in 1.7 l water	Na^+ 106 mmol/l, Cl^- 78 mmol/l, CO_3^{2-} 14 mmol/l
1832: Latta's solution 2[10]	2–3 drachms muriate of soda, 2 scruples subcarbonate of soda, 6 pints of water	Na^+ 164–230 mmol, Cl^- 133–199 mmol, HCO_3^- 31 mmol, in 3.4 l water	Na^+ 48–68 mmol/l, Cl^- 39–59 mmol/l, HCO_3^- 9 mmol/l
1832: Craigie's solution[22]	1 drachm muriate of soda, 10 grains carbonate of soda, 2 pounds aqua calid	Na^+ 77 mmol, Cl^- 66 mmol, CO_3^{2-} 6 mmol, in 746 ml hot water	Na^+ 103 mmol/l, Cl^- 88 mmol/l, CO_3^{2-} 8 mmol/l
1832: Meikle's solution[32]	4 drachms muriate of soda, 4 scruples carbonate of soda, 2 ounces albumen, 10 pounds water	Na^+ 365 mmol, Cl^- 267 mmol, CO_3^{2-} 49 mmol, Albumen 62.2 g, in 3.73 l water	Na^+ 98 mmol/l, Cl^- 72 mmol/l, CO_3^{2-} 13 mmol/l, albumen 17 g/l
1832: Latta's solution 3[30]	Half drachm muriate of soda, 8 grains subcarbonate of soda, 1 pound water saturated with protoxide of azote	Na^+ 40 mmol, Cl^- 34 mmol, HCO_3^- 6 mmol, in 373 ml of water saturated with 'laughing gas'	Na^+ 107 mmol/l, Cl^- 91 mmol/l, HCO_3^- 16 mmol/l
1832: Latta's solution 4[31]	''... the solution I used contained a third more saline matter ...''	Na^+ 50 mmol, Cl^- 44 mmol, HCO_3^- 6 mmol, in 373 ml water saturated with 'laughing gas'	Na^+ 134 mmol/l, Cl^- 118 mmol/l, HCO_3^- 16 mmol/l
1849: Henry Howlett's solution[27]	1 drachm common salt, half drachm sulphate of potash, 1 quart water	Na^+ 66 mmol, Cl^- 66 mmol, K^+ 22 mmol, SO_4^{2-} 11 mmol, in 1.14 l water	Na^+ 58 mmol/l, Cl^- 58 mmol/l, K^+ 19 mmol/l, SO_4^{2-} 10 mmol/l
1853: Owen Rees' solution[35]	3 ounces chloride of sodium, one ounce phosphate of soda, One and a half ounces carbonate of soda, half ounce sulphate of soda, small portions of distilled water added to make solution of specific gravity 1030	Na^+ 3.13 mol, Cl^- 1.59 mol, PO_4^{2-} 220 mmol, CO_3^{2-}440 mmol, SO_4^{2-}110 mmol, in xxx distilled water	As the volume of water used is not known, we are unable to calculate the concentrations of the various anions and cations
1866: Murchison's solution[34]	One and a half drachms chloride of sodium, half drachm chloride of potassium, 10 grains phosphate of soda, 5 grains carbonate of soda, 2 pints of water	Na^+ 114 mmol, Cl^- 126 mmol, K^+ 26 mmol, PO_4^{2-} 4 mmol, CO_3^{2-} 3 mmol, in 1.136 l water	Na^+ 130 mmol/l, Cl^- 143 mmol/l, K^+ 29 mmol/l, PO_4^{2-} 4.5 mmol/l, CO_3^{2-} 3.4 mmol/l
1871: Marsden's solution[3]	3 drachms chloride of sodium, half drachm subcarbonate of soda, 15 grains potassium chloride, 48 ounces water	Na^+ 234 mmol, Cl^- 210 mmol, K^+ 12 mmol, HCO_3^- 18 mmol, in 1.363 l water	Na^+ 162 mmol/l, Cl^- 154 mmol/l, K^+ 12 mmol/l, HCO_3^- 17 mmol/l
1879: Kronecker and Sander's solution[29,a]	6 grams cooking salt, 0.05 grams sodium hydroxide, in 1 litre distilled water	Na^+ 104 mmol, Cl^- 103 mmol, OH^- 1 mmol, in 1 litre distilled water	Na^+ 104 mmol/l, Cl^- 103 mmol/l, OH^- 1 mmol/l
1883: Egerton Jenning's solution[28]	50 grains chloride of sodium, 3 grains chloride of potassium, 25 grains sulphate of soda, 25 grains carbonate of soda, 2 grains phosphate of soda (Na_3PO_4), 2 drachms absolute alcohol, in 20 ounces of water	Na^+ 109.4 mmol, Cl^- 58 mmol, K^+ 5 mmol, SO_4^{2-} 11 mmol, CO_3^{2-} 15 mmol, PO_4^{2-} 1 mmol, alcohol 7 ml, in 568 ml water	Na^+ 190 mmol/l, Cl^- 101 mmol/l, K^+ 5 mmol/l, SO_4^{2-} 19 mmol/l, CO_3^{2-} 26 mmol/l, PO_4^{2-} 2 mmol/l, 12 ml alcohol
1883: Szumann's solution[26]	6 g common salt, 1 g sodic carbonate, in 1000 g distilled water	Na^+ 122 mmol, Cl^- 103 mmol, CO_3^{2-} 9 mmol, in 1 l water	Na^+ 122 mmol/l, Cl^- 103 mmol/l, CO_3^{2-} 9 mmol/l
1883: Ringer's solution[37,b]	6 g sodium chloride, 3.1 g sodium lactate, 300 mg potassium chloride and 200 mg calcium chloride in 1000 ml water	Na^+ 130 mmol, K^+ 4 mmol, Ca^{2+} 1.5 mmol, Cl^- 109 mmol, $C_3H_5O_3^-$ (lactate) 28 mmol, in 1 l water	Na^+ 130 mmol/l, K^+ 4 mmol/l, Ca^{2+} 1.5 mmol/l, Cl^- 109 mmol/l, $C_3H_5O_3^-$ (lactate) 28 mmol/l

1888: Churton's solution[39]	3 drachms of chloride of sodium, 18 grains of chlorate of potash, 9 grains of phosphate of soda, and 60 grains of bicarbonate of soda, in 3 pints of distilled water	Na^+ 256 mmol, Cl^- 219 mmol, PO_4^{2-} 4.2 mmol, HCO_3^- 46 mmol, in 1705 ml water	Na^+ 150 mmol, Cl^- 128 mmol, PO_4^{2-} 2.5 mmol, HCO_3^- 27 mmol
1891: Richardson's solution[36]	30 grains chloride of sodium, 15 grains phosphate of soda, 1 pint distilled water	Na^+ 43 mmol, Cl^- 31 mmol, PO_4^{2-} 6 mmol, in 568 ml water	Na^+ 76 mmol/l, Cl^- 55 mmol/l, PO_4^{2-} 11 mmol/l
1892: Pye-Smith's solution[40]	1 drachm of common salt to 1 pint of recently boiled water	Na^+ 66 mmol, Cl^- 66 mmol, in 568 ml water	Na^+ 116 mmol/l, Cl^- 116 mmol/l
1898: Thelwall Thomas's solution[41]	6 parts of sodium chloride to 1000 parts of sterilised water	Na^+ 103 mmol, Cl^- 103 mmol, in 1000 ml water	Na^+ 103 mmol/l, Cl^- 103 mmol/l
1932: Hartmann's solution[38,51–53]	6 g sodium chloride, 3.22 g sodium lactate, 400 mg potassium chloride and 270 mg calcium chloride in 1000 ml water	Na^+ 131 mmol, K^+ 5 mmol, Ca^{2+} 2 mmol, Cl^- 111 mmol, $C_3H_5O_3^-$ (lactate) 29 mmol, in 1 l water	Na^+ 131 mmol/l, K^+ 5 mmol/l, Ca^{2+} 2 mmol/l, Cl^- 111 mmol/l, $C_3H_5O_3^-$ (lactate) 29 mmol/l
0.9% sodium chloride	9 g sodium chloride in 1 l water	Na^+ 154 mmol, Cl^- 154 mmol, in 1 l water	Na^+ 154 mmol/l, Cl^- 154 mmol/l

[a] Reference obtained from Foex.[6]
[b] Conversion obtained from Miller.[33]

'Indifferent', 'physiological' or 'normal' saline

Interest in the composition of salt solutions was given further impetus by 19th century studies of isolated frog nerve and muscle. Perhaps the best known of these were performed by Sydney Ringer[33,37,42,49,50] which led to the development and subsequent modification of Ringer's solution, the basis of the modern solutions such as Hartmann's.[37,38,51–53] Ringer set out to ''ascertain the influence each constituent of the blood exercises on the contraction of the ventricle''[37] and, having bathed frog heart muscle preparations in solutions of different constituents, found that a 0.75% saline solution ''makes an excellent circulating fluid in experiments with the detached heart''. He later discovered that the saline solution previously used was made using pipe water supplied by the New River Water Company and not distilled water as intended.[37] On repeating the experiments he found that bathing the heart muscle in saline solution made with distilled water made the ventricle grow ''weaker and weaker'' leading to cessation of contractility in about 20 min. He concluded that the effects he had previously obtained were ''due to some of the inorganic constituents of the pipe water''.[37] Ringer's solution (Table 3) was developed as a consequence of these observations and later modified by Alexis Hartmann who added sodium lactate to it with the aim of reducing the acidosis seen in infants suffering from diarrhoea, dehydration and oliguria.[53]

Three decades prior to Ringer's experiments, Koelliker had observed that nerve and muscle preserved their irritability and appearance for many hours in solutions of 0.5–1% sodium chloride which he therefore termed 'indifferent' solutions.[54] Nasse later determined the optimal concentration of salt for the preservation of the irritability of tissues was 0.6%. Hermann designated this solution 'physiological water'.[55] The term 'physiological salt solution' appears to have been popularised after observations that transfusions of this solution were capable of saving the lives of animals and humans after profuse haemorrhage.[55]

By the late 19th century, with better understanding of the principles of membrane permeability, osmosis and fluid tonicity, it was realised that for the fluid to be 'indifferent' it also had to be isotonic with the serum. The 0.6% solution was isotonic with the serum of the frog and was therefore only 'indifferent' or 'physiological' in this animal. Hamburger later found that a more concentrated solution was needed for isotonicity with mammalian serum.[56] However, as Joseph and Meltzer stated in 1911,[55] ''The consequences of these new conceptions found their way into practice only slowly, and even to this day the subject is frequently handled in a loose fashion''.

The first recorded use of the term 'normal saline' appeared in a report published in the Lancet on 29th September 1888.[39] This described a case of 'scirrhus of the pylorus' treated at Leeds General Infirmary by Dr. Churton. The patient had suffered over a month of vomiting, with minimal oral intake leading him to become ''moribund ... prostrate and pulseless'' when ''he was ordered transfusion of 'normal saline' solution in order to replace the fluid thus lost''. The patient was injected with 34 fluid ounces of

this fluid, which bore no resemblance to 0.9% saline (Table 3), with immediate improvement in his condition. Repeated injections resulted in continued improvement.

Churton[39] mentions that ''the success of transfusion of the so-called normal saline solution to replace the lost water and salts of the blood was more permanent than in cholera, where there is a poison; or in cases of haemorrhage and anaemia, where blood cells are also wanting ... it is probable that by the intravenous injection of a saline solution, or a mixture of such a solution with blood, strength might be obtained to endure or to rally after an operation (of any kind) from which some exhausted patients could not otherwise recover''. Spencer first used the term 'normal salt' solution in 1892,[57,58] but failed to describe the composition of this fluid. These authors[39,57,58] made no mention of the origins of the terms 'normal saline' or 'normal salt', but one may speculate that, as the terms were put in quotation marks, they may have been a colloquialism current at the time rather than having any scientific basis.

The reassuring terms 'normal' and 'physiological', now commonly applied to 0.9% saline, while having no scientific validity, may have aided its widespread acceptance in practice, despite the fact that it is neither chemically normal, implying a concentration of 58.5 g NaCl/l, nor physiological, i.e. similar to extracellular fluid.[59]

Hamburger: forgotten father of 0.9% saline?

None of the intravenous saline solutions described between 1832 and 1895 bear any resemblance to 0.9% saline (Table 3). The first reference to a solution similar to 0.9% saline appeared in 1896.[60] In his article W.S. Lazarus-Barlow cites Hamburger as the main authority for suggesting that a concentration of 0.92% saline was 'normal' for mammalian blood.[60]

Hartog Jakob Hamburger was a Dutch physiological chemist, appointed lecturer in physiology and pathology at the Utrecht Veterinary School in 1888.[61] Although remembered for his 'phenomenon' (the chloride shift); his 'interchange' (secondary buffering), and his 'law' (which states that when blood is rendered acid, albumins and phosphates pass from the red blood corpuscles to the serum and the chlorides pass from the serum to the cells) no mention is made in his obituary[61] of his role in the evolution of saline solutions. In a lecture delivered at the University of London and published in the Lancet of 19th November 1921, Hamburger[56] refers to his own work which ''alas, has of late been too often overlooked''. He was originally inspired by the work of the botanist Hugo de Vries in 1882 on the force with which plant cells attract water.[62] A year later Hamburger performed experiments on the effect of solutions, with varying concentrations of salt, on the escape of colouring matter from erythrocytes.[63] He found that ''for every salt a concentration could be obtained in which the least resistant blood corpuscles lost their colouring matter'' and speculated that ''the salt solutions used caused a swelling which a number of the blood corpuscles could not withstand without losing their colouring matter''.

It is accepted that the freezing point of human serum is $-0.52\,^{\circ}$C. Hamburger, after comparing the ''freezing-points'' of serum obtained from animals and human subjects, concluded that ''the blood of the majority of warm-blooded animals, including man, was isotonic with a NaCl solution of 0.9 per cent., and not of 0.6 per cent., as was generally thought ... and which had always been called the physiological NaCl solution''.[56] His theory linking the isotonicity of 0.9% saline to human blood, although credibly backed by his experimental evidence, was not universally accepted.[60] The scientific evidence supporting the use of 0.9% saline in clinical practice seems to be based solely on this *in vitro* study. It remains a mystery how it came into general use as an intravenous fluid *in vivo*. Perhaps it was due to the ease, convenience and low cost of mixing common salt with water.

Acceptance into routine practice and modern day problems: abnormal saline

Fluid therapy with saline solutions, in the form of proctoclysis and hypodermoclysis, became routine in the early 20th century. In 1911 Evans[64] stated his intention to ''sound a note of warning against the thoughtless and indiscriminate use of this remedy'' and to dispel the erroneous belief that the administration of 'sodium chlorid' solutions was harmless just because the salt was present in all foodstuffs, in body fluids, and incorrectly thought to be readily excreted by the kidneys. Having highlighted the dangers of salt overload and retention he urged restricting its use to ''those conditions in which either quantitative or qualitative changes in the blood-plasma present logical indications for its application'' and where ''circulatory or renal contra-indications do not exist''. It would appear, from subsequent literature, that Evans' plea for caution fell on deaf ears.

On the other hand, the value of salt solution given appropriately is apparent from the study by Hartwell and Hoguet[65] on experimental intestinal obstruction in dogs and its treatment by subcutaneous infusions of 'normal saline', which laid the foundations for saline therapy in patients with intestinal obstruction.

In 1913 Trout[66] reported a study of postoperative fluid replacement by proctoclysis in some 2000 patients treated at 232 hospitals, who were allocated to receive either tap water or 'normal' saline enemas. Whilst Trout acknowledged some flaws in the experimental design, this was nonetheless the first scientific study of the management of postoperative fluid balance. Trout calculated that, using normal saline, ''we would be forcing into an already weakened patient, in the space of 24 hours, the average amount of salt consumed as a condiment by a normal man in one month''. He also noted transient albuminuria, using saline, which disappeared 24 h after water was substituted, returning again on further use of saline. Trout concluded ''surgeons have simply drifted into employing salt solution by rectum without giving any serious consideration to what they were doing, and such is our excuse for this paper''.

A decade later Rudolph Matas, regarded as the originator of modern fluid therapy,[2] introduced the concept of 'the continued intravenous drip',[67] but also warned of the potential dangers of saline infusions. He referred to work by Roessle who showed organic changes in human heart muscle after saline infusions, by Hoeszli who noted degenerative changes in the heart and kidneys of guinea-pigs 6–7 h after

massive saline infusions, and by Thiess who in 1910 pointed out ''that a healthy man needs 17 gm. of salt per day, but receives 27 gm. when given 3 litres of 0.9 per cent. salt solution ... part of the salt is eliminated by the kidneys, but some is retained in tissues, where it attracts liquids and causes oedema''.[68] Matas concluded for the above reasons that his preferred solution was 5% glucose rather than saline.

In 1936 Coller et al.[69] studied three groups of postoperative patients who received 5% dextrose in either a ''solution of sodium chloride, in Ringer's solution or in distilled water''. Although they used a 'physiologic solution of sodium chloride' containing 8.5 g NaCl/l, they again found fluid retention, when saline solutions were given intravenously to sick surgical patients, in contrast to 5% dextrose which was excreted more rapidly.

Fluid retention in postoperative patients, receiving crystalloid infusions, is exacerbated by their diminished ability to excrete an excess sodium and water load.[70–74] This classical feature of the metabolic response to injury is unfortunately sometimes forgotten.[75–77] That such fluid retention is not innocuous is shown by the work of several authors who have described an increase in postoperative complications and adverse outcomes associated with excess sodium and water administration in the perioperative period.[77–87]

Even healthy volunteers have difficulty with saline.[88–91] When 2-l infusions administered over 1 h of either 0.9% saline or Hartmann's solution were compared, at 6 h 56% of the infused saline was retained in contrast to only 30% of the Hartmann's solution.[91] A marked and sustained hyperchloraemia was also seen following saline infusion. Infusion of large volumes of saline in healthy volunteers have also been shown to produce abdominal discomfort and pain, nausea, drowsiness and decreased mental capacity to perform complex tasks.[92]

The persistent hyperchloraemia after saline infusions[91–98] reflects the lower $[Na^+]$:$[Cl^-]$ ratio in saline (1:1) than in Hartmann's solution (1.18:1) or plasma (1.38:1).[93] While infusions of 0.9% saline produce a significant hyperchloraemic acidosis, infusions of Hartmann's solution do not significantly alter bicarbonate and chloride concentrations or pH.[91,94] The decrease in the anion gap is more pronounced with saline than with Hartmann's solution and reflects the differential fall in serum albumin concentration.[91,94] As the negatively charged albumin molecule accounts for about 75% of the anion gap,[99] the acute dilutional hypoalbuminaemia produced by crystalloid infusions[91,96] can reduce the anion gap by 2.5 mmol/l for every 10 g/l fall in serum albumin concentration in critically ill patients.[100,101] Stewart[102] has described a mathematical approach to acid base balance in which the strong ion difference ($[Na^+] + [K^+] - [Cl^-]$) is the major determinant of the H^+ ion concentration. A decrease in the strong ion difference is associated with a metabolic acidosis and an increase with a metabolic alkalosis. Chloride concentration is the major anionic contributor to H^+ homeostasis and hyperchloraemia decreases the strong ion difference, resulting in a metabolic acidosis.[91,94,96,100,103–105]

Veech[93] has emphasised that the kidney is slow to excrete an excess chloride load after the infusion of large amounts of saline. Wilcox found, in animal studies, that sustained renal vasoconstriction was related to hyperchloraemia, which was potentiated by previous salt depletion and related to the tubular reabsorption of chloride[106] which appeared to be initiated by an intrarenal mechanism and was accompanied by a reduction in glomerular filtration rate. Wilcox also established that, although changes in renal blood flow and glomerular filtration rate were independent of changes in the fractional reabsorption of sodium, they correlated well with changes in the fractional reabsorption of chloride, suggesting that renal vascular resistance was related to the delivery of chloride, but not sodium, to the loop of Henle.[106] Chloride-induced vasoconstriction appeared to be specific for the renal vessels, so that the regulation of renal blood flow and glomerular filtration rate by chloride could override the effects of hyperosmolality on the renal circulation.[106] Further studies on young adult men have shown that plasma renin activity is suppressed 30 and 60 min after infusion of sodium chloride, but not after infusion of sodium bicarbonate, suggesting that both the renin and blood pressure responses to sodium chloride are dependent on chloride.[107] Hyperchloraemic acidosis, as a result of saline infusions has also been shown to reduce gastric blood flow and decrease gastric intramucosal pH in elderly surgical patients,[97] and both respiratory and metabolic acidosis have been associated with impaired gastric motility in pigs.[108] In patients undergoing colonic surgery, salt and water overload delayed recovery of gastrointestinal function,[83] increased complications and prolonged hospital stay.[83,84] Acidosis also impairs cardiac contractility and may decrease the response to inotropes.

At the cellular level, salt and water overload can result in cytosolic acidification, membrane hyperpolarisation, inactivation of protein kinases and disruption of phosphorylation, leading to cellular dysfunction.[109] In addition, there is increasing evidence that 0.9% sodium chloride solution has adverse effects on immune cells. Although *in vitro* studies have demonstrated that 0.9% sodium chloride solution causes activation of human neutrophils,[110] an effect on neutrophil function was not demonstrated in a study in which healthy human volunteers were infused with 2 l of 0.9% saline.[111] Recent animal models of haemorrhagic shock that employed 0.9% sodium chloride as a resuscitation fluid found this led to significant pulmonary inflammatory infiltrates and decreased oxygenation.[112] It has been suggested that the use of 0.9% sodium chloride may exacerbate injury-related neutrophil activation, thus predisposing the host to infectious complications.[113]

Alexis Hartmann, in 1934, suggested that his lactated Ringer's solution was superior to saline infusions in the treatment of infantile diarrhoea.[38] Subsequent publications have confirmed its superiority for resuscitation,[94,95,97,114] which may be partly due to the lower chloride concentration of Hartmann's solution as well as its buffering properties.

Whilst there is no doubt that saline infusions have saved a number of lives in medical and surgical practice, this could well have been achieved by a balanced crystalloid, with fewer side effects. Evans[64] put this into perspective by commenting that, ''One cannot fail to be impressed with the danger ... (of) the utter recklessness with which salt solution is frequently prescribed, particularly in the postoperative period.'' and going on to state that, ''... the

disastrous role played by the salt solution is often lost in light of the serious conditions that call forth its use.''

The attempt to find a truly physiological crystalloid preparation for both scientific and clinical work has been going on for 175 years and the results have inevitably been a compromise. In conditions of peripheral circulatory failure or liver disease, there may be increased endogenous lactate production or decreased capacity to metabolise infused lactate.[93] On the other hand, the unphysiological proportion of chloride in 0.9% saline causes other problems as outlined. There seems to be no historical or scientific basis, except for Hamburger's *in vitro* studies of red cell lysis,[56] to support the continued use of 0.9% saline in clinical practice save in cases involving large chloride losses, e.g. due to vomiting. It is also extremely doubtful that, if a range of intravenous fluids were being designed today on evidence-based principles, 0.9% saline would figure prominently. A fresh look at crystalloid formulae is overdue. In the meantime there is a strong case for using solutions nearer in composition to Ringer's lactate or Hartmann's solution rather than 0.9% saline, in most patients requiring more than 1000—1500 ml of crystalloid solution per day for resuscitation or replacement.

Conflict of interest statement

None of the authors has a conflict of interest to declare.

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